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(54) Title: COMPOUNDS AND COMPOSITIONS FOR ADMINISTRATION VIA ORAL INHALATION OR INSUFFLATION

(57) Abstract

5-Acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid exhibits antiviral activity in animals, in particular in humans, when administered by mouth via inhalation or insufflation.

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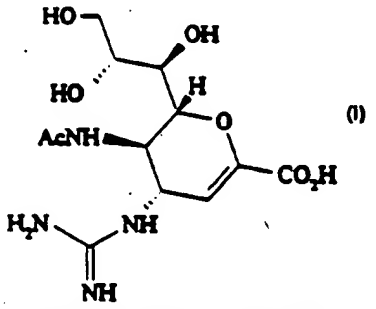
COMPOUNDS AND COMPOSITIONS FOR ADMINISTRATION VIA ORAL INHALATION OR INSUFFLATION

The present invention relates to administration of medicaments by mouth via inhalation or insufflation.

PCT/AU91/00161 (publication no. WO91/16320) describes a number of derivatives of 5-acetamidino-2,3,5-trideoxy-D-glycero-D-galacto-non-2-enopyranosonic acid (2,3,-dideoxy-2,3-didehydro-N-acetyl-neuraminic acid; DANA) including the 4-guanidino analogue of DANA, which has the following structure:



(I)

4-guanidino analogue of DANA

and the chemical name 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid, and is also known as GG167.

The compound of formula (I) has antiviral activity. In particular, this compound is an inhibitor of viral neuraminidase, for example, the viral neuraminidase of influenza A and B.

Pharmaceutical formulations, in particular formulations for intranasal administration, are also described in WO91/16320.

We have now found that the compound of formula (I) exhibits antiviral activity in animals, in particular in humans, when administered by mouth via inhalation or insufflation.

In a first aspect, the present invention accordingly provides a method of treatment of an animal, including man, suffering from or susceptible to a viral infection, in particular an influenza virus infection, which method comprises administration to said animal of an effective amount of the compound of formula (I) by inhalation or insufflation through the mouth.

In a second or alternative aspect, the invention provides the use of the compound of formula (I) for the manufacture of a medicament adapted for inhalation or insufflation through the mouth for the treatment of a viral infection.

For administration according to the method of the invention, the compound of formula (I) may be administered by any of the methods and formulations employed in the art for administration by inhalation or insufflation through the mouth.

Thus in general the compound of formula (I) may be administered to the lung in the form of a solution or a suspension or a dry powder. The compound of formula (I) may be micronised or non-micronised. The delivery systems currently available e.g. pressurised metered dose inhalers, nebulisers and dry powder inhalers, are suitable for administration according to the invention. It is anticipated that any system developed in the future for the delivery of dry powder, solution or suspension by inhalation via the mouth will also be suitable.

The present invention provides a pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising the compound of formula (I) and a pharmaceutically acceptable carrier therefor.

When desired the formulations may be adapted to give sustained release of the active ingredient.

Solutions and suspensions may be aqueous, for example prepared from water alone (for example sterile or pyrogen - free water), or water and a physiologically

acceptable co-solvent (e.g. ethanol, propylene glycol or a polyethylene glycol such as PEG 400). Alternatively, solutions and suspensions may be non-aqueous, for example prepared from organic solvents such as chlorofluorocarbons and fluorocarbons, for example 1,1,1,2 - tetrafluoroethane.

Such solutions and suspensions may additionally contain other excipients for example preservatives (such as benzalkonium chloride), solubilising agents/surfactants such as polysorbates (e.g. Tween 80, Span 80 or lecithins), buffering agents, isotonicity - adjusting agents (e.g. sodium chloride or sugars) and absorption enhancers. Suspensions may additionally contain suspending agents (e.g. microcrystalline cellulose, carboxymethyl cellulose sodium).

Solutions may be preserved or may be aseptically prepared or sterilised after manufacture using conventional methods.

For administration according to the invention, the compound of formula (I) is preferably administered by means of a dry powder inhaler. This method of administration provides particularly rapid delivery of GG167 to the lung.

When the compound of formula (I) is provided in the form of a dry powder, it may be presented alone or in admixture with a suitable pharmaceutically acceptable diluent such as starch, starch derivatives such as hydroxypropylmethyl cellulose or polyvinylpyrrolidine (PVP), sugar derivatives such as mannitol or, preferably, lactose. The powder composition may be presented in unit dose form, for example in capsules or cartridges of e.g. gelatin or formed plastic or blister packs from which the powder may be administered by means of an inhalation device, or in multidose form from, for example, a powder reservoir.

Suitable inhalation devices include those described in EP 069715, GB 2041763, WO91/13646, GB 1561835, GB 2064336, GB 2129691, GB 2178965 or GB 2242134. A preferred inhalation device for administration in accordance with the invention is the DISKHALER (trade mark). Devices may deliver single or multiple doses.

Dry powder inhalers are designed to deliver a fixed unit dosage of medicament per actuation. When the compound of formula (I) is administered by means of a dry powder inhaler it will suitably be administered in an amount of 0.01 to 25mg, such as 0.5 to 20mg per actuation, for example 0.1 to 10mg per actuation, preferably about 5mg or about 10mg per actuation.

It will be appreciated that the precise dose administered will depend on the age and condition of the patient and the frequency of administration and will ultimately be at the discretion of the attendant physician. Typically, administration may be one or more times, for example 1 to 8 times per day, giving for example 1, 2, 3 or 4 unit doses each time.

We have found that it is particularly advantageous to administer the compound of formula (I) to a patient using a combination of intranasal administration and inhalation or insufflation via the mouth. For use in combination with inhalation of insufflation via the mouth, intranasal administration may be effected using any of the methods known in the art for intranasal administration of pharmaceuticals and, in particular, any of the methods described in WO91/16320. Thus, for example, the compound of formula (I) may be applied to nasal cavity as a solution, a suspension or a dry powder. Solutions and suspensions may be administered intranasally using, for example, a pipette, a dropper or a spray. Dry powders may be administered intranasally by inhalation, for example, using an inhaler.

A preferred method of combined administration comprises inhalation or insufflation by mouth of GG167 in the form of a dry powder and administration of a solution or suspension of GG167 to the nasal cavity as a spray.

For combined administration, GG167 may be administered by inhalation or insufflation via the mouth and by intranasal administration either simultaneously (i.e. within 10 minutes of each other, such as within about 5 minutes of each other) or separately. Typically GG167 may be administered by inhalation or insufflation via the mouth from 1 to 8 times daily and by intranasal administration from 1 to 8 times daily. Preferably administration via the mouth and intranasal administration will take place essentially simultaneously.

The invention is further illustrated by the following examples.

Example 1

A double-blind, randomised, placebo-controlled study was conducted in adult human patients all of whom had had symptoms of influenza-like illness (including feverishness and at least two of myalgia, headache, cough, sore throat) for up to 48 hours.

Patients were randomised to receive one of the following treatments for 5 days:

1. GG167 (5mg per inhalation) two oral inhalations twice a day plus placebo two sprays per nostril (0.1ml per spray) twice a day.

2. GG167 (5mg per inhalation) two oral inhalations twice a day plus GG167 (16mg/ml) two sprays per nostril (0.1ml per spray) twice a day.

3. Placebo two oral inhalations twice a day plus placebo two sprays per nostril (0.1ml per spray) twice a day.

GG167 was presented as the formulation of Example 3 using a DISKHALER (trade mark).

The results indicated that GG167 has antiviral activity against influenza virus when administered by inhalation via the mouth alone or in combination with intranasal administration.

Example 2

Safety

A double-blind, randomised, placebo-controlled study was conducted in two phases. All treatments were administered to 20 healthy male subjects via a nebuliser.

Single-Dose Phase: Eight subjects, aged 18 - 39 years (average 26.5 years, average weight 74.6kg), received single ascending doses of 4mg, 8mg or 16mg GG167 or randomised placebo.

Multiple-Dose Phase: Twelve subjects, aged 19 - 45 years (average 28 years, average 75.8kg), received the highest safe and well-tolerated dose as determined in the first phase (i.e. 16mg), or placebo, with up to four administrations per day for 7 days.

GG167, at doses up to 64mg per day, was safe and well tolerated when administered by nebuliser.

Example 3

Dry Powder Formulation

Compound of formula (I) (micronised)	5mg
Lactose	to 25mg

The formulation is prepared by admixture of the ingredients using conventional pharmaceutical techniques.

CLAIMS

1. A method of treatment of an animal, including man, suffering from or susceptible to a viral infection which method comprises administration to said animal of an effective amount of 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid by inhalation or insufflation through the mouth.

2. The method as claimed in claim 1 wherein the viral infection is an influenza virus infection.

3. The method as claimed in claim 1 or claim 2 wherein the 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid is administered in the form of a dry powder free from excipients.

4. The method as claimed in any one of claims 1 to 3 further comprising intranasal administration of 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid.

5. The method as claimed in claim 4 wherein administration by inhalation or insufflation through the mouth and intranasal administration are essentially simultaneous.

6. A pharmaceutical composition adapted for administration by inhalation or insufflation through the mouth comprising 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid and a pharmaceutically acceptable carrier therefor.

7. A composition as claimed in claim 6 in the form of a solution or suspension.

8. A composition as claimed in claim 6 in the form of a dry powder.

9. A composition as claimed in claim 8 presented in a capsule or cartridge.

10. A method of treatment of an animal, including man, suffering from or susceptible to a viral infection which method comprises administration to said animal of an effective amount of a composition as claimed in any one of claims 6 to 9.

11. The use of 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid for the manufacture of a medicament adapted for administration by inhalation or insufflation through the mouth .

12. The use as claimed in claim 11 wherein the medicament is 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid in the form of a dry powder free from excipients.

13. A process for the preparation of a pharmaceutical composition as claimed in any one of claims 6 to 9 which process comprises admixture of 5-acetamido-2,3,4,5-tetradeoxy-4-guanidino-D-glycero-D-galacto-non-2-enopyranosonic acid with a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 95/01967

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 539 204 (BIOTA SCIENTIFIC MANAGEMENT PTY. LTD) 28 April 1993 see page 2, line 1 - line 3 see page 4, line 38 - page 6, line 42 see page 3, line 1 - line 16	1-13
Y	WO,A,91 16320 (BIOTA SCIENTIFIC MANAGEMENT PTY LTD) 31 October 1991 cited in the application see page 9, line 21 - page 11, line 24; claims 1-6	1-13
Y	EP,A,0 341 735 (MECT CORPORATION) 15 November 1989 see abstract see page 3, line 19 - line 20	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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...information on patent family members

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